

Translation

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>HF 002/2003 PCT</b>	<b>FOR FURTHER ACTION</b>	
		See Form PCT/IPEA/416
International application No. <b>PCT/EP2004/000485</b>	International filing date ( <i>day/month/year</i> ) <b>22.01.2004</b>	Priority date ( <i>day/month/year</i> ) <b>03.02.2003</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D 487/04</b>		
Applicant <b>HF ARZNEIMITTELFORSCHUNG GMBH</b>		

<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <b>4</b> sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> (<i>sent to the applicant and to the International Bureau</i>) a total of _____ sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>																									
<p>4. This report contains indications relating to the following items:</p> <table style="margin-left: 20px;"> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>		<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/	Authorized officer
Facsimile No.	Telephone No.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/EP2004/000485

## Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- This report is based on translations from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of:
- international search (Rule 12.3 and 23.1(b))
  - publication of the international application (Rule 12.4)
  - international preliminary examination (Rule 55.2 and/or 55.3)
2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):
- the international application as originally filed/furnished
- the description:  
pages 1-13 as originally filed/furnished  
pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_  
pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- the claims:  
nos. 1-22 as originally filed/furnished  
nos.\* \_\_\_\_\_ as amended (together with any statement) under Article 19  
nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_  
nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- the drawings:  
sheets \_\_\_\_\_ as originally filed/furnished  
sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_  
sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.
3.  The amendments have resulted in the cancellation of:
- the description, pages \_\_\_\_\_
  - the claims, nos. \_\_\_\_\_
  - the drawings, sheets/figs \_\_\_\_\_
  - the sequence listing (*specify*): \_\_\_\_\_
  - any table(s) related to sequence listing (*specify*): \_\_\_\_\_
4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- the description, pages \_\_\_\_\_
  - the claims, nos. \_\_\_\_\_
  - the drawings, sheets/figs \_\_\_\_\_
  - the sequence listing (*specify*): \_\_\_\_\_
  - any table(s) related to sequence listing (*specify*): \_\_\_\_\_

\* If item 4 applies, some or all of those sheets may be marked "superseded."

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/EP2004/000485

Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
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## 1. Statement

Novelty (N)	Claims	1-22	YES
	Claims		NO
Inventive step (IS)	Claims	1-22	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-22	YES
	Claims		NO

## 2. Citations and explanations (Rule 70.7)

This report is based on the following documents, which were cited in the search report:

D1: JEN, T. ET AL.: "Amidines. 5. Synthesis of Pyrrolo[2,3-b]isoquinoline, Imidazo[1,2-b]isoquinoline, Pyrrolo[2,1-b]quinazoline, and 1,3-Thiazino[2,3-b]quinazoline Derivatives and Related Heterocycles as Potential Antihypertensive Agents" JOURNAL OF MEDICINAL CHEMISTRY, vol. 16, no. 6, 1973, pages 633-637

D2: YADAV, J.S.; REDDY, B.V.S.: "Microwave-assisted rapid synthesis of the cytotoxic alkaloid luotonin A" TETRAHEDRON LETTERS, vol. 43, 2002, pages 1905-1907

D3: SPATH, E.; PLATZER, N.: "Über Derivate des Peganins und ihre Ring-Homologen" CHEMISCHE BERICHTE, 1935, pages 2221-2226

The present application pertains to a process for preparing 1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline (compound III) by reducing the keto precursor (I) obtained by reacting isatoic anhydride (II) with an

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International application No.  
PCT/EP2004/000485

Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
	excess of 2-pyrrolidone (claims 1-17, 22).

Further, the application pertains to a process whereby compound III is liberated in molten form from the salt as a free base.

Although D2 and D3 describe processes for reacting 2-pyrrolidone with compound II, said processes always involve the use of equimolar amounts of the two constituents. D1 describes a process (schema III) for preparing compound III using *o*-aminobenzylamines and gamma-butyrolactone. Therefore, the novelty (PCT Article 33(2)) of claims 1-22 should be acknowledged.

The description contains experimental data which show the use of a molar excess of 2-pyrrolidone to be advantageous, in particular with respect to achievable yields (cf. example 1, 21% and example 2, 55%). Although this should be considered a logical consequence of equilibrium shift, the fact that compound I (pegenon) can be obtained without 2-pyrrolidone contamination in crystallized form must be considered surprising. The requirements of PCT Article 33(3) are met.